REMARKS

Claims 2 and 40-72 are pending in this application. Claims 1 and 3-39 have been cancelled. Claim 2 has been amended to further define the invention. The amendments find support in the application and originally filed claims. For example, support for the additions to claim 2 can be found in original claim 1 from which claim 2 originally depended. Support for "single amplification reaction" can be found at p. 15, paragraph [0042]. Support for a "single polymerase chain reaction" can be found in original claim 2 and on p. 10, paragraph [0029]. Support for the detection clause in claims 2, 54, 62 and 67 is found throughout the application and in Figure 1. Support for new claims 40-72 can be found, for example, in original claims 1, 3-11, 13-16, 19-27, 29-34 and 36-39. Accordingly, the present amendments and new claims raise no issue of new matter.

Claim Objection

The Examiner's assertion that claim 12 fails to further limit subject matter already present in claim 2 is acknowledged. However, the objection has been rendered moot by cancellation of claim 12.

Rejection under 35 U.S.C. § 112

The Examiner's assertion that there is insufficient antecedent basis for the limitation of "the live tissue sample" in claim 8 is acknowledged. However, the rejection has been rendered moot by cancellation of claim 8.

Rejections under 35 U.S.C. § 102

Rejection under 35 U.S.C. § 102(b) over Lindpainter, et al.

The rejection of claims 1, 3-10, 13, 34 and 36-37 under 35 U.S.C. §102(b), as allegedly being anticipated by Lindpainter, et al. (NEJM 1195, VOL. 332, NO. 11, P. 706-11), is

acknowledged. However, the rejection has been rendered moot by cancellation of claims 1, 3-10, 13, 34 and 36-37.

Rejection under 35 U.S.C. § 102(b) over Teranishi, et al.

The rejection of claims 1, 3-10, 13, 34 and 36-37 under 35 §102(b), as allegedly being anticipated by Teranishi et al. (Journal of Hypertension, 1999, vol. 17, p. 351-56), is acknowledged. However, the rejection has been rendered moot by cancellation of claims 1, 3-10, 13, 34 and 36-37.

Rejection under 35 U.S.C. § 102(a) over Lin, et al.

The rejection of claims 1-10, 12-13 and 34-37 as allegedly being anticipated by Lin, et al. (Clinical Biochemistry, 2001, vol. 34, p. 661-66) is respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990); *see also*, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. Only once a prima facie case has been established does the burden shift to the applicant to rebut the prima facie case. *See, e.g., In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Claims 1, 3-10, 12, 34 and 37 have been cancelled. Claims 3-10, 34 and 37 although cancelled, are similar to new claims 41-48, 68 and 71 directed to genotyping using three primers in a single amplification reaction in combination with detecting one or two amplification products for a homozygous genotype and three amplification products for a heterozygous genotype. The rejection will be addressed with respect to all these claims.

Lin does not disclose all claim elements because Lin fails to detect three amplification products for a heterozygous ACE genotype. Rather, Lin only discloses the detection of one or two amplification products for both homozygous and heterozygous genotypes.

Applicant takes issue with the Examiner's assertion that Figure 2 of Lin discloses detection of three amplification products to determine a genotype. Office Action p. 11, lines 18-21. In reference to Figure 2, Lin clearly states that "two melting peaks" were analyzed. *See* header "3. Results" on p. 662. Applicant confirms that only two peaks are visible in Figure 2. Thus, this evidence in Lin fails to disclose a single amplification reaction with the detection of three amplification products.

Applicant also takes issue with the Examiner's assertion that Figure 3A of Lin discloses detection of three amplification products to determine a genotype. Office Action p. 11, lines 18-21. With respect to Figure 3A, only two peaks were detected and Applicant confirms that only two peaks are visible. *See* header "3. Results" on p. 662-663. The only difference in Figure 2 and Figure 3A appears to be that the conditions of Figure 3A are optimized to equalize the intensity of the two peaks. Thus, this evidence in Lin fails to disclose a single amplification reaction with the detection of three amplification products.

Applicant further takes issue with the Examiner's assertion that Figure 3B of Lin discloses detection of three amplification products to determine a genotype. With respect to Figure 3B, which is the visualization of the PCR products from Figure 3A on an agarose gel, Applicant notes that the agarose gel does contain three bands. However, the third band is not an amplification product from an ACE gene template. Rather, the third band is simply an assay artifact which the authors labeled as "Primer." One of ordinary skill in the art would recognize that this third band is not amplification of an ACE gene template but rather a product of primer-primer interaction. Thus, this evidence in Lin fails to disclose a single amplification reaction with the detection of three amplification products.

Applicant also takes issue with the Examiner's assertion that a single PCR reaction resulting in the amplification of three products is mentioned by Lin in the section on p. 662 titled "Genotyping of ACE gene I/D allele by conventional PCR." Office Action p. 11, lines 20-21 (citing a "490, 190 and undisclosed 3rd amplicon size"). Although this section of Lin discloses detection of three amplification products, multiple amplification reactions were needed to

achieve this result. Lin, p. 662, col. 2, lines 7-13. Thus, this evidence in Lin also fails to disclose a single amplification reaction with the detection of three amplification products.

The Examiner has asserted multiple instances of evidence in Lin of a single reaction with the detection of three amplification products. However, a proper reading of Lin as a whole fails to support such assertion. Thus, novelty is present and Applicant respectfully requests reconsideration and withdrawal of the rejection. If the Examiner should sustain the novelty rejection over Lin, Applicant requests that the Examiner point out where each of the three alleged amplification products are shown for a single amplification reaction.

Rejections under 35 U.S.C. § 103

Rejection under 35 U.S.C. § 103(a) over Lindpainter, et al. in view of Soubrier, et al. and further in view of Buck, et al.

The rejection of claims 11, 14-16, 19, 21-26 and 38-39 as being obvious over Lindpainter, et al. in view of Soubrier, et al. (U.S. Patent No. 5,736,323; April 1998) and further in view of Buck, et al. (Biotechniques, 1999, vol. 27(3), p. 528-536) is acknowledged. However, the rejection has been rendered moot by cancellation of claims 11, 14-16, 19, 21-26 and 38-39.

Rejection under 35 U.S.C. § 103(a) over Lindpainter, et al. in view of van Bockxmeer, et al.

The rejection of claims 29-32 as being obvious over Lindpainter, et al. in view of van Bockxmeer, et al. (Circulation, 1995, vol. 92, p. 2066-71) is acknowledged. However, the rejection has been rendered moot by cancellation of claims 29-32.

Rejection under 35 U.S.C. § 103(a) over Lindpainter et al. in view of Soubrier et al., further in view of Buck, et al. and further in of Lin, et al.

The rejection of claim 20 as being obvious over Lindpainter, et al. in view of Soubrier, et al., further in view of Buck, et al. and further in view of Lin, et al. is respectfully traversed. Claim 20 has been cancelled. Applicant respectfully submits that this rejection has been

rendered moot with respect to this claim. Applicant however, will address this rejection with respect to all of the pending claims since all claims now require using three primers in a single amplification reaction in combination with detecting one or two amplification products for a homozygous genotype and three amplification products for a heterozygous genotype.

To establish a prima facie case of obviousness, three criteria must be met; (1) there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; (2) there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and (3) the publications must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2142.

As discussed in detail above, the claims are directed to a method of genotyping employing a single amplification reaction using three primers and then determining the genotype by detecting up to three amplification products. In contrast, the assay of Lindpainter requires multiple amplification reactions and the use of four different primers. *See* header "Determination of ACE Genotypes" on p. 707, column 2. Soubrier is unable to cure the deficiency of Lindpainter because Soubrier merely teaches possible primers that can be used in an ACE genotyping assay and says nothing about how to achieve an assay with a single amplification reaction using three primers that allows detection of one or two products for a homozygous ACE genotype and three amplification products for a heterozygous ACE genotype. Buck is also unable to cure the deficiencies of Lindpainter and/or Soubrier because Buck merely teaches sequencing primer design which is not even relevant to the present invention.

The Examiner apparently agrees to these deficiencies by stating "neither Lindpainter or Soubrier teach a step where the amplification comprises performing a single PCR amplification reaction." *See* Office Action p. 25, lines 8-10. The Examiner then turns to Lin to address the gap in the rejection. However as discussed in the 102 rejection above, Lin does not disclose a single amplification reaction using three primers and detecting three amplification products. Rather, Lin only discloses the detection of one or two amplification products for both homozygous and

heterozygous genotypes. The Examiner is reminded that "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." *In re Kahn*, 441 F.3d 977, 986 (Fed Cir. 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

Furthermore, there would be no motivation to combine the four references because Lindpainter and Lin deal with the same problem in different ways. Both Lindpainter and Lin are focusing on detection of two amplification products and are struggling to achieve clear distinction of both products in one system. *See* Lindpainter, p. 707, col. 2, lines 34-35; and Lin, p. 662, col. 2, lines 3-6. Page 707 of Lindpainter addresses the problem by performing multiple PCR reactions, while Lin at p. 661-663 addresses the problem by designing primers so that the two amplification products are of similar length and by altering primer concentrations. Thus one of ordinary skill in the art would not be motivated to combine disparate solutions to one problem to achieve a solution to an entirely different problem. Instead, one of ordinary skill in the art would likely choose either the Lindpainter or Lin but not both.

Moreover, there would be no reasonable expectation of success because both Lindpainter and Lin struggle to solve the problem of preferential amplification in only a dual product amplification format. *See* Lindpainter, header "Determination of ACE Genotypes" on p. 707; and Lin, header "Genotyping of ACE gene I/D allele by conventional PCR" on p. 662. Thus, there would be no reasonable expectation of success in modifying these efforts to achieve a more complex three product format from a single amplification reaction.

Applicant also wishes to point out that multiplex PCR was well known in the art since the late 1980s, well before the time of Lindpainter and Lin. Yet up until the time of Applicant's invention, many years later, no one, even those of above ordinary skill in the art such as Lindpainter and Lin, combined a single amplification with the detection of three amplification products as required by the instant claims. Thus, because the cited references alone or in combination fail to provide a prima facie case of obviousness, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Relevant Prior Art

The prior art made of record by the Examiner of Shanmugam, et al. (PCR Methods and Application, 1993, vol. 3, p. 120-121); Odawara, et al. (Human Genetics, 1997, vol. 100, p. 163-66); Montgomery, et al. (Circulation, 1997, vol. 96, p. 741-47), Frishberg, et al. (Kidney International, 1998, vol. 54, p. 1843-2849); Pederson-Bjergaard, et al. (U.S. Patent Application No. 20030158090 (2003)); and Osterop, et al. (Hypertension, 1998, vol. 32, p. 825-30) is acknowledged. These references are not addressed by Applicant because no rejection has been formulated.

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CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date June 23, 2006

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